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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/353,423	07/15/99	NAGABHUSHAN T	CJ-0776QK

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EXAMINER	
BAKER, A	
ART UNIT	**PAPER NUMBER**
1632	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/353,423	Applicant(s) NAGABHUSHAN ET AL.	
	Examiner Anne-Marie Baker	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,13-17 and 19-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,13-17 and 19-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 July 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

File

DETAILED ACTION

The amendments filed April 9, 2001 and May 18, 2001 (Paper Nos. 6 and 8) have been entered. Claims 1 and 13 have been amended. Claims 5, 10, 11, 12, and 18 have been cancelled.

Claims 1-4, 6-9, 13-17, and 19-39 remain pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-9, 13-17, and 19-39 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-9 of the previous Office Action mailed 10/4/00 (Paper No. 5), as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-4 and 6-9 are directed to a method for treating a patient suffering from a disease by administering a viral vector encoding an interferon α (IFNα) polypeptide. Claims 13-17 are directed to a method for expressing interferon α in a patient. Claims 19-29 are directed to a recombinant vector comprising a nucleic acid segment encoding an interferon α polypeptide, wherein the interferon α polypeptide lacks a secretion leader sequence. Claims 30-33 are directed to a pharmaceutical formulation comprising a

recombinant vector comprising a nucleic acid segment encoding an interferon α polypeptide, wherein the interferon α polypeptide lacks a secretion leader sequence. Claims 34-39 are directed to a method of treating hepatocellular carcinoma in a mammal.

At the outset the Examiner notes that Applicants have mistaken the rejection set forth under 35 U.S.C. 112, first paragraph, as a written description rejection (p. 3 of the response). However, the rejection is based on a failure to comply with the enablement requirement.

At page 5 of the response, Applicants state that they believe that the Examiner is not questioning the utility under 35 U.S.C. 101 of the claimed compositions. To clarify, the Examiner accepts that gene therapy is a credible utility for the methods and compositions of the invention. However, it is the **only** utility asserted in the specification and the specification does not **enable** the use of the methods and compositions for gene therapy. While the specification suggests various dosages, routes of administration, and vectors individually, there is no guidance as to those combinations of these parameters that provides or correlates to a therapeutic effect where a symptom is alleviated by IFNα production in a patient. For the reasons discussed in the previous Office Action (Paper No. 5), undue experimentation would have been required for the skilled artisan to practice the claimed methods and make and use the claimed compositions.

At pages 7-9 of the response, Applicants argue that the level of skill in the art of molecular biology and medicine is high. At page 8, Applicants state that they believe that the high level of skill and knowledge in this art are such that a rather limited disclosure would enable one of skill in the art to practice the full scope of the claimed invention. At page 9, Applicants assert that a significant quantity of data can be obtained with relative ease. However, in the art of gene therapy intensive investigation is required to enable even a single embodiment for treatment of a specific disease. The courts have held that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may

not be workable. A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) and *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CAFC 1997) citing *Brenner v. Manson*. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification only provides a starting point, a direction for further research. *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (CAFC 1997), *cert. denied*, 118 S. Ct. 397 (1997).

At pages 9-11 of the response, Applicants argue that the level of predictability in the art of gene therapy is much greater than is reflected in the references cited by the Examiner. Applicants argue that these references do not provide a fair characterization of the state of the art as can be seen from other publications. Applicant argues that the views of Dr. Crystal and Dr. Verma must have changed over time because their opinions expressed in the review articles are contradicted by their opinions expressed in their issued patents. However, Applicants have not pointed to any particular opinions expressed in these issued patents which reflect that their views have changed and the Examiner does not find that the mere fact that they have obtained patents for vectors and gene delivery methods contradicts their view that gene therapy is unpredictable in a global arena. Furthermore, the patents which Applicants cite do not enable the instant invention. Specific gene therapies with sufficient guidance that removes the art taught unpredictabilities certainly would meet the enablement provisions.

At page 11 of the response, Applicants argue that the Deonarian reference cited by the Examiner actually focuses on the promise of non-viral polyplex targeted delivery of DNA. However, the instant invention is limited to the use of viral vectors and does not employ non-viral polyplex targeted delivery of DNA. Further, citing page 65 of the Deonarian reference, Applicants provide a quote which discusses "good

prospects," "progressing well," and points to techniques which "may prove" to be effective. However, neither optimism or "good prospects" are sufficient to enable the claimed invention as it is well-established that the invention must be enabled at the time of filing. A potential for future successes in gene therapy does not constitute enablement, but rather is suggestive of a technology that is still undeveloped. One of skill in the art would conclude that the development of gene therapy protocols is not routine if potential successes lie predominantly in the future, not in the past. This emphasizes the need for specific guidance from the specification at the time of filing.

At page 11 of the response, Applicants again state that they believe that the high levels of skill and knowledge in this art are such that a rather limited disclosure would enable one of skill in the art to practice the full scope of the claimed invention. For reasons of record, the Examiner does not agree. As the specification does not offer specific guidance for carrying out the claimed methods for the treatment of any disease, and the specification further does not teach the direction in which experimentation should proceed, undue experimentation clearly would have been required for one skilled in the art to develop appropriate protocols to practice the claimed methods and to use the claimed compositions.

At page 12 of the response, Applicants argue that specific information is provided regarding dosage regimens at page 20, line 12 through page 22, line 25 of the specification. However, the specification does not teach how to use the claimed invention to achieve the requisite level of IFNα to produce a therapeutic effect in an immunocompetent animal using the disclosure of dosage regimes.

At pages 12-13 of the response, Applicants argue that adenoviral vectors can be repeatedly administered to a mammal and still provide an acceptable safety profile and transgene expression. While the Examiner acknowledges that re-administration can be performed, the instant specification does not provide a correlation for achieving therapeutic levels of IFNα with any such protocol. Applicants argue that a number

of scientific studies in human beings provide a great deal of guidance to the skilled artisan in the specifics of route of administration and dosage regimens which are acceptable in the human being. Applicants cite several references from 1998, 1999, and 2001. However, the priority date of this application is 1996, and thus the guidance available from these studies was not available at the time of filing. It is well-established that the invention must be enabled at the time of filing. Post-filing art cannot be used to supplement the teachings of the disclosure for enablement purposes. Post-filing art must be supported by the specification in order to be persuasive.

Further, as discussed on pages 6-7 of the previous Office Action (Paper No. 5), it is noted that nude mouse tumor models are not predictive of results obtainable in immunocompetent animals. At page 14 of the response, Applicants argue that the examples of *in vivo* efficacy in immunodeficient mice supplied in the instant application do provide correlation to the clinical utility of the compositions of the present invention. However, Applicants have not addressed the arguments regarding the lack of predictive success for nude mouse models.

At pages 14-19 of the response, Applicants discuss numerous patents that have issued, which Applicants believe have broad claims for limited disclosure. First, each patent application is examined on the basis of its own merits, considering as a whole all the evidence presented. The specification itself need not be the sole source of the evidence presented. Second, Applicants seem to be under the impression that the Examiner has suggested that the **claims** should be limited to particular routes of administration, dosage range, delivery system, etc. However, this is not the case. The rejection is based, in part, on the lack of **disclosure** of such parameters appropriate for producing a therapeutic effect in an immunocompetent animal. While the specification suggests various dosages, routes of administration, vectors, and promoters that could be used, it does not provide specific guidance regarding the combinations that will produce the desired effect.

There is no correlation on the record for combining any dosage amount with any route of delivery or viral vector construct to achieve any type of therapeutic effect associated with IFNα production. The specification does not provide sufficient specific guidance to the skilled artisan for developing protocols for the various disease states as contemplated (see p. 4 of the previous Office Action). Absent sufficient disclosure, the skilled artisan would be left to determine the various combinations of parameters that would result in producing a therapeutic effect. However, the specification does not teach the direction in which experimentation should proceed and undue experimentation would have been required to develop appropriate protocols for the numerous disease states.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-9, 13-17 and 34-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-9 are indefinite as they depend from cancelled Claim 5.

Claims 13-17 are indefinite because there appears to be a typographical error in lines 1, 3, and 4 of Claim 13, where the claim recites "interferon a" rather than "interferon α" in the clean version of the claims.

Claim 13 is indefinite in its recitation of "[a] method for expressing interferon α levels" because it is unclear how "levels" are expressed. Claim language reciting "[a] method for expressing interferon α polypeptide" is suggested. Claims 14-17 are indefinite in so far as they depend from Claim 13.

Claims 34-39 are indefinite because the method does not recite that the administration of the vector results in any effect, such as treatment, as recited in the preamble. The preamble recites "a method of treating hepatocellular carcinoma," but the method does not provide for any such effect, but rather only involves the administration of a vector.

At page 3 of the response, Applicants argue that they have amended Claim 34 to recite that a therapeutic effect is achieved. However, Claim 34 has not been amended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The rejection of Claims 1-4, 10, 11, 13, 14, 17, and 18 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,069,133 (Chiou et al., 2000) is withdrawn in view of Applicants' amendment limiting the claims to the use of viral vectors.

Given that the term "patient" is not defined in the specification, the term is interpreted as broadly as reasonable. Therefore, the following art rejection is set forth with the understanding that the term "patient" reads broadly on any mammal, e.g. any mammal involved in an experimental or clinical trial, whether healthy or unhealthy. The enablement rejection set forth above is only directed to enablement for the asserted utility

of gene therapy. Thus, while the specification is not enabling for the only asserted utility, the claims read broadly on methods of *in vivo* gene delivery and do not recite a therapeutic effect.

Claims 1-3 and 6-9 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,935,935 (Connelly et al.).

Connelly et al. disclose adenoviral vectors encoding interferon α for *in vivo* gene delivery. See Column 11, lines 29-36. At Column 7, lines 35-40, the specification discloses the use of tissue-specific promoters in these vectors, including liver-specific promoters such as the albumin promoter. The disclosure teaches the use of such vectors *in vivo* for the expression of therapeutic genes (Example 13). The adenoviral vector may be replication competent or replication defective (see Column 10, lines 17-35). It is noted that Claims 1-3 and 6-9 do not recite a therapeutic effect, but rather only require that the interferon α polypeptide be expressed at any level.

Thus, the claimed method is disclosed in the prior art.

Conclusion

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and

any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne-Marie Baker, Ph.D.

Deborah Crouch

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PRIMARY EXAMINER
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